Notes

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Iodinated Benzamidotetrazoles

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Many iodinated benzoic acids have been prepared to be used as x-ray diagnostic agents. One of the main difficulties is to obtain a compound that is both soluble and non-toxic. In an attempt to accomplish this, several iodinated benzoic acids were converted to the corresponding iodinated benzamidotetrazoles *via* their acid chlorides.

Ettel and Nosek[1] have prepared several substituted benzamidotetrazoles by this method but none containing iodine.

EXPERIMENTAL[2]

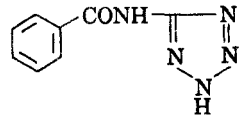
All of the iodinated benzoic acids were prepared as reported by Goldberg.[3]

Iodinated benzamidotetrazole. A mixture of iodinated benzoic acid (0.1 mole) and thionyl chloride (300 ml.) was heated under reflux for 1 hr. The resultant clear yellow solution was evaporated to dryness on a steam bath under vacuum. The residue was crystallized from *n*-heptane. Yields of the acid chloride were nearly quantitative.

Equimolar amounts of the acid chloride and 5-aminotetrazole were suspended in dry benzene (100 ml. benzene/0.01 mole tetrazole) and refluxed for 24 hr. During this time a fine white crystalline precipitate formed which was collected and washed well with water. It was dissolved by suspending in water and adding an equivalent of sodium hydroxide. After decolorizing with charcoal and filtering, the solution was acidified with acetic acid and the white product collected and dried in a vacuum oven at 110° C. Fifty to seventy-five percent yields were obtained.

The solubilities of the sodium salts of the tetrazoles were found to be equal to or greater than those of the corresponding sodium salts of the iodinated benzoic acids.

TABLE I
IODINATED BENZAMIDOTETRAZOLES



Substituents	M.P., °C.	Formula	Carbon		Hydrogen		Iodine		Toxicities[a] ALD_{50}	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	T	B
3,4-Diiodo-	266.7–271.3	$C_8H_5I_2N_5O$	21.78	21.89	1.14	1.99	57.57	57.00	>200	225
3,5-Diiodo-	295.8–297.7	$C_8H_5I_2N_5O$	21.78	21.64	1.14	1.61	57.57	58.10	300	180
2,5-Diiodo-	>300	$C_8H_5I_2N_5O$	21.78	21.77	1.14	1.33	57.57	57.90	900	500
3,5-Diiodo-4-hydroxy-	252.0–258.0	$C_8H_5I_2N_5O_2$	21.02	21.13	1.10	1.11	55.54	55.20	950	750
3,5-Diiodo-2-hydroxy-	234.4–234.9	$C_8H_5I_2N_5O_2$	21.02	20.96	1.10	1.30	55.54	55.30	300	...
3,5-Diiodo-2-methoxy-	243.2–243.6	$C_9H_7I_2N_5O_2$	22.95	23.13	1.50	1.88	53.90	53.60	360	360
3,5-Diiodo-4-methoxy-	224.5–228.0	$C_9H_7I_2N_5O_2$	22.95	23.10	1.50	1.47	53.90	53.80	450	300
3,4,5-Triiodo-	>300	$C_8H_4I_3N_5O$	16.95	17.26	0.71	0.94	67.17	66.70	250	>160
2,3,5-Triiodo-	>300	$C_8H_4I_3N_5O$	16.95	16.74	0.71	0.84	67.17	66.30	250	>200

[a] Toxicities were run in mice intravenously. The column headed by T shows the toxicities of the tetrazoles and the column headed by B shows the toxicities of the corresponding iodinated benzoic acids.

When administered intravenously as the sodium salt to cats at dose levels of 200–400 mg./kg. of body weight, the gall bladder was outlined in x-ray photographs.

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(1) V. Ettel and J. Nosek, *Coll. Czechoslov. Chem. Communs.*, **15**, 335 (1950).

(2) All melting points are corrected. Analyses were carried out by Messrs. M. E. Auerbach, K. D. Fleischer, and staff.

(3) A. Goldberg *et al.*, *Quart. J. and Yearbook of Pharmacy*, **19**, 483 (1946).

N-Substitution Products of 2-Aminomethyl-1,4-benzodioxane

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Benzodioxane and phenyl alkylamine ethers are among the classes of compounds which have been shown to exhibit adrenergic blocking activity.[2–4] In the search for a more nearly perfect sympatholytic drug, an investigation was initiated on a series of compounds which link 2-methyl-1,4-benzodioxane with a phenyl alkylamine ether. Several *N*-substitution products of 2-aminomethyl-1,4-benzodioxane have been previously synthesized. *N*,*N*-Diethyl- and *N*-methyl-2-aminomethyl-1,4-benzodioxane have been prepared by heating diethylamine and methylamine respectively with 2-chloromethyl-1,4-

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(2) D. Bovet and A. Simon, *Compt. Rend. Biol.*, **116**, 842 (1934).

(3) D. Bovet and A. Simon, *Arch. Intern. Pharmacodynamic*, **55**, 15 (1937).

(4) R. B. Barlow, *Introduction to Chemical Pharmacology*. John Wiley and Sons, Inc., New York, N. Y., 1955, p. 242.

benzodioxane under pressure for 5 hr. at 140–150°.[5] These two compounds were also synthesized by heating the same reactants in a sealed tube at 175° for 2 hr.[6] 2-(1-Piperidyl)methyl-1,4-benzodioxane[7] was prepared by treating piperidine with 2-chloromethyl-1,4-benzodioxane. 2-(Tetrahydro-*p*-oxazinyl)methyl-1,4-benzodioxane[8] was prepared by heating 2-chloromethyl-1,4-benzodioxane with morpholine in an autoclave at 150° for 10–12 hr. Only a few preparations have been described for substitution products of 2-aminomethyl-1,4-benzodioxane which have two dissimilar groups attached to the nitrogen. Kerwin[9] prepared *N*-(2-hydroxyethyl)-*N*-ethyl-2-aminomethyl-1,4-benzodioxane by refluxing 2-ethylaminoethanol and 2-chloromethyl-1,4-benzodioxane in xylene for 13.5 hr. The chloro derivative was obtained by treating the reaction product with thionyl chloride. Kerwin also prepared *N*-benzyl, *N*-methylallyl, and *N*-cyclohexyl derivatives of *N*-(2-hydroxyethyl)-2-aminomethyl-1,4-benzodioxane by similar methods.

A tabulation of *N*-substitution products of 2-aminomethyl-1,4-benzodioxane reported in the literature to date reveals 31 such compounds of a secondary or tertiary type. All the compounds were prepared by the reaction of 2-chloromethyl-1,4-benzodioxane with an amine. Grum[10] has reported that the ester of an organic acid and 2-hydroxymethyl-1,4-benzodioxane will react with amines to form these products.

The preparation of reasonably pure secondary amines by the reaction of a halide and amine is subject to the disadvantage that some higher substitution inevitably occurs. Wheeler and Wilson[11] have outlined a procedure for *N*-phenylbenzylamine which minimizes disubstitution. This is accomplished by slowly adding the halide to a large excess of amine. In addition to inhibiting disubstitution, the excess primary amine ties up the hydrogen halide liberated by the reaction.

This study is concerned with the development of a procedure for the synthesis of a series of tertiary amines having a *N*-substituted alkyl aryl ether on *N*-benzyl-2-aminomethyl-1,4-benzodioxane. Specifically, the object was to synthesize and characterize *N*-benzyl-2-aminomethyl-1,4-benzodioxane, *N*-(2-phenoxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane, and *N*-(2-*o*-toloxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane. Suitable starting materials for these syntheses appeared to be 2-chloromethyl-1,4-benzodioxane,[6] 2-phenoxyethyl bromide,[12] 2-*o*-toloxyethyl bromide,[12] and benzyl amine, the first three of which were prepared by published methods and the fourth is readily available commercially. As a result *N*-benzyl-2-aminomethyl-1,4-benzodioxane has been synthesized and characterized for the first time. The formation and characterization of two derivatives of the same, namely the benzoyl and the benzenesulfonyl, further support the identification of the compound. Two corresponding tertiary amines, *i.e.*, the 2-phenoxyethyl and 2-*o*-toloxyethyl are also reported for the first time.

The preparation of *N*-benzyl-2-aminomethyl-1,4-benzodioxane was also attempted by the use of inert organic solvents, *i.e.*, ether and toluene, but results were less satisfactory. The reactant, benzylamine, was found to be the most satisfactory solvent for the reaction. The excess benzylamine combined with the hydrogen chloride liberated in the reaction, thus eliminating the need for an additional base in the reaction mixture, and greatly simplified the isolation of the desired compound. Separation of the excess primary and desired secondary amine was facilitated by the relative insolubility of the hydrochloride salt of *N*-benzyl-2-aminomethyl-1,4-benzodioxane in cold water. Little residue was left after distillation of the secondary amine, indicating that the formation of a tertiary amine was negligible under the conditions employed. *N*-Benzyl-2-aminomethyl-1,4-benzodioxane reacted, at room temperature, with benzoyl chloride and benzenesulfonyl chloride without the addition of another base. However, satisfactory yields were not obtained until the reaction mixtures were heated and an excess of the acid halides were used.

N-Benzyl-2-aminomethyl-1,4-benzodioxane was found to be a suitable intermediate for the synthesis of *N*-(2-phenoxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane and *N*-(2-*o*-toloxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane. When an excess of the parent secondary amine was stirred with phenoxyethyl bromide or *o*-toloxyethyl bromide, a reaction took place as soon as the temperature of the mixture reached 100°, and was complete after 6 hr. More drastic conditions produced some decomposition and less drastic resulted in incomplete reaction. The addition of another organic base to combine with the hydrogen bromide liberated in the reaction should increase the yield of tertiary amine in terms of the parent secondary amine. In the procedure employed, however, the hydrobromide salt of *N*-benzyl-2-aminomethyl-1,4-benzodioxane is easily recovered for reuse and the purification of the final tertiary amine is greatly simplified.

The viscous oil consistency of *N*-(2-phenoxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane and *N*-(2-*o*-toloxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane make final purification by recrys-

(5) E. Fourneau, Mm. de Lestrange, and P. Maderni, *J. Pharm. chim.*, **18**, 185 (1933).

(6) J. Trefouel, Mme. J. Trefouel, and Y. Dunant, *Bull. Sci. Pharmacol*, **42**, 459 (1935).

(7) E. Forneau, U. S. Patent **2,056,046** (1936).

(8) A. Green, U. S. Patent **2,366,102** (1944).

(9) J. F. Kerwin, U. S. Patent **2,551,013** (1951).

(10) A. Grum, U. S. Patent **2,366,102** (1944).

(11) T. Wheeler and T. Wilson, *Org. Syntheses*, **Coll. Vol. I**, 102 (1941).

(12) C. S. Marvel and A. L. Tannenbaum, *Org. Syntheses*, **Coll. Vol. I**, 436 (1941).

tallization from common organic solvents impractical. Distillation of these compounds had to be performed below 1 mm. to prevent decomposition.

As a result of this study, five new secondary or tertiary amines and related derivatives have been prepared and characterized for the first time. The findings also indicate that other *N*-substituted alkyl-aryl ether derivatives of *N*-benzyl-2-aminomethyl-1,4-benzodioxane can be prepared by the method developed in the preparation of the original members of this series.

EXPERIMENTAL

N-Benzyl-2-aminomethyl-1,4-benzodioxane. A 36.8 g. (0.2 mole) portion of 2-chloromethyl-1,4-benzodioxane was added dropwise with stirring, under reflux, during 2.5 hr. to 85.6 g. (0.8 mole) of benzylamine; the mixture was refluxed an additional 1.5 hr., and then cooled to room temperature. Upon the addition of 200 g. of 6*N* hydrochloric acid, a precipitate of secondary amine hydrochloride was obtained. This precipitate was collected and washed with water and ether to remove the excess benzylamine hydrochloride and other impurities. The crude product was then recrystallized from hot water. The free secondary amine was obtained as a viscous oil by neutralization of the hydrochloride salt with sodium bicarbonate. The oil was extracted with ether and the ether then removed by evaporation. The residue was distilled at 180–200° in a Hickmann molecular still at 1 mm. pressure. The yield was 36 g. (70.5%) of a clear viscous liquid with d_4^{25} of 1.1448 and n_D^{25} of 1.5778. Upon prolonged cooling the compound solidified to a white crystalline product, melting at 41°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.3; H, 6.67; N, 5.59; M.R., 74.7; mol. wt. 255. Found: C, 75.6; H, 6.98; N, 5.49; M.R. 75.6; mol. wt. 253.

The hydrochloride salt melted at 185° and the hydrobromide salt melted at 214°.

The benzoyl and the benzenesulfonyl derivatives of *N*-benzyl-2-aminomethyl-1,4-benzodioxane, were prepared for further characterization of the above compound. A 5.1 g. (0.02 mole) portion of *N*-benzyl-2-aminomethyl-1,4-benzodioxane was stirred for 0.5 hr. with 5.2 g. (0.04 mole) of benzoyl chloride at 100°, 30 ml. of 10% aqueous sodium hydroxide was then added and the heating continued for an additional 1.5 hr. Upon cooling, the sodium hydroxide solution was decanted, and the remaining precipitate was washed three times with 30 ml. portions of 10% aqueous sodium hydroxide. The remaining product was dissolved in 30 ml. of ether, the solution washed first with 6*N* hydrochloric acid and then with water, and finally dried over anhydrous sodium sulfate. The resulting solution was filtered, the ether evaporated, and the residue distilled at 0.05 mm. in a Hickmann molecular still, at 250–60°, yielding a slightly yellow, extremely viscous oil that solidified below −5°, and had n_D^{25} of 1.5895.

Anal. Calcd. for $C_{23}H_{21}O_3N$: C, 76.88; H, 5.85; N, 3.90; mol. wt. 359. Found: C, 76.53; H, 5.56; N, 4.19; mol. wt. 353.

The benzenesulfonyl derivative was similarly prepared by stirring 5.1 g. (0.02 mole) of *N*-benzyl-2-aminomethyl-1,4-benzodioxane at 100° for 0.5 hr. with 7.1 g. (0.04 mole) of benzenesulfonyl chloride. Thirty ml. of 10% aqueous sodium hydroxide was then added and the heating continued for an additional 1.5 hr. Upon cooling, the sodium hydroxide solution was decanted, and the residue washed three times with 30 ml. portions of 10% aqueous sodium hydroxide. The remaining product was dissolved in 30 ml. of ether, the solution washed first with 6*N* hydrochloric acid, then with water, and finally the ether evaporated. The residue changed from a yellow oil to a white crystalline product when warmed with ethanol. The crystals were triturated several times with ethanol and water and dried, yielding a final derivative melting at 84°.

Anal. Calcd. for $C_{22}H_{21}O_4N$: C, 66.84; H, 5.32; N, 3.54; mol. wt. 395. Found: C, 66.86; H, 5.24; N, 3.73; mol. wt. 399.

N-(2-Phenoxyethyl)-N-benzyl-2-aminomethyl-1,4-benzodioxane. A 10.8 g. (0.04 mole) portion of *N*-benzyl-2-aminomethyl-1,4-benzodioxane and 6 g. (0.03 mole) of phenoxyethyl bromide was heated with stirring at 120° for 6 hr. The reaction mixture was then cooled and triturated with ether and the ether mixture filtered to remove the hydrobromide salt of *N*-benzyl-2-aminomethyl-1,4-benzodioxane. Upon the addition of 20 ml. of 6*N* hydrochloric acid, the hydrochloride salt of *N*-(2-phenoxyethyl)-*N*-benzyl-2-aminomethyl-1,4-benzodioxane separated from the ether as a slightly yellow, very viscous oil. After the salt had been washed with water and ether, it was heated in water and treated with sodium bicarbonate to release the free amine. The free amine was extracted from the mixture with ether, the ether solution washed with water, dried over anhydrous sodium sulfate and filtered. The ether was distilled off, and the residue distilled at 220–240°, in a Hickmann molecular still at 0.05 mm., yielding a pale yellow viscous liquid with n_D^{27} of 1.5820, and d_4^{27} of 1.1415 and which solidified to a white crystalline solid on prolonged standing and melted at 43°.

Anal. Calcd. for $C_{24}H_{25}O_3N$: C, 76.80; H, 6.67; N, 3.73; M.R. 108.9; mol. wt. 375. Found: C, 76.97; H, 6.87; N, 3.38; M.R. 108.76; mol. wt. 372.

N-(2-o-Toloxyethyl)-N-benzyl-2-aminomethyl-1,4-benzodioxane. This compound was prepared and purified by a procedure similar to that described immediately above for N-(2-phenoxyethyl)-N-benzyl-2-aminomethyl-1,4-benzodioxane, except *o*-toloxyethyl bromide was used in place of phenoxyethyl bromide. The product was a pale yellow viscous oil, with a n_D^{27} of 1.5790, and d_4^{27} of 1.1342.

Anal. Calcd. for $C_{25}H_{27}O_3N$: C, 77.12; H, 6.94; N, 3.60; M.R., 113.5; mol. wt. 389. Found: C, 77.47; H, 6.55; N, 3.32; M.R., 112.7; mol. wt. 384.

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Studies in the Pyrazole Series. IX.[1] Aminolytic and Substitution Reactions of 3,5-Dimethyl-1-(*N*,*N*-diphenylcarbamyl)-pyrazole

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While the solvolytic deacylation reactions of 1-guanyl- and related pyrazoles[1] have been ascribed to a so-called $B_{AC}2$ type[3] mechanism, no unequivocal evidence has been obtained to exclude from

(1) Part VIII: F. L. Scott, *J. Org. Chem.*, 22, 1568 (1957).

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(3) See C. K. Ingold, *Structure and Mechanisms in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 752 *et seq.*, wherein the $B_{AC}2$ mechanism is defined as a base-induced bimolecular hydrolysis of esters with acyl scission.